

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and

I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **COMPOSITIONS AND METHODS FOR ENHANCED BIOSTABILITY AND ALTERED BIODISTRIBUTION OF OLIGONUCLEOTIDES IN MAMMALS** the specification of which:

() is attached hereto.

(XX) was filed on September 12, 1997 as Application Serial No. 08/928,823 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to the patentability of this application in accordance with 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of any application on which priority is claimed:

Country	Number	Date Filed	Priority Claimed
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status
Serial No. 08/464,953	June 5, 1995,	Pending
Serial No. 08/117,363	September 3, 1993	Pending
Serial No. PCT/US92/09196	October 23, 1992	Abandoned
Serial No. 08/211,882,	April 22, 1994	Pending
Serial No. 07/782,374	October 24, 1991	Abandoned
Serial No. 07/463,358	January 11, 1990	Abandoned
Serial No. 07/566,977	August 13, 1990	Abandoned
Serial No. 08/344,155	November 23, 1994	
Serial No. 08/063,167	May 17, 1993	U.S. Patent No. 5,514,788
Serial No. 08/007,997	January 21, 1993	U.S. Patent No. 5,591,623
Serial No. 07/939,855	September 2, 1992	Abandoned
Serial No. 07/567,286	August 14, 1990	Abandoned
Serial No. 08/731,299	October 4, 1996	

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: **John W. Caldwell** and **Michael P Straher**, Registration Nos. 28,937 and 38,325 of the firm of **WOODCOCK WASHBURN KURTZ MACKIEWICZ & NORRIS LLP**, One Liberty Place - 46th Floor, Philadelphia, Pennsylvania 19103, and **Herb Boswell**, **Laurel Bernstein** and **Andrew E. Granston**, Registration Nos. 27,311, 37,280 and 38,473, of **ISIS Pharmaceuticals**, 2292 Faraday Avenue, Carlsbad, California 92008.

Address all telephone calls and correspondence to:

John W. Caldwell
WOODCOCK WASHBURN KURTZ MACKIEWICZ & NORRIS LLP
 One Liberty Place - 46th Floor

Philadelphia, PA 19103
Telephone No. 215-568-3100.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1	Full Name: Phillip Dan Cook	Inventor's Signature: <i>Phillip Dan Cook</i>	Date: 12/11/97
	Residence: Escondido, California	Citizenship: USA	
	Post Office Address: 2124 Acker Way Escondido, CA 92029		
2	Full Name: Dr. Muthiah Manoharan	Inventor's Signature: <i>Muthiah Manoharan</i>	Date 12/11/97
	Residence: Carlsbad, California	Citizenship: USA	
	Post Office Address: 7634 Reposado Drive Carlsbad, CA 92009		
3	Full Name: Clarence Frank Bennett	Inventor's Signature: <i>C. Frank Bennett</i>	Date 11-21-97
	Residence: Carlsbad, California	Citizenship: USA	
	Post Office Address: 1347 Cassins Street Carlsbad, CA 92009		

**RECEIVED BY THE UNITED STATES PATENT AND
TRADEMARK OFFICE**

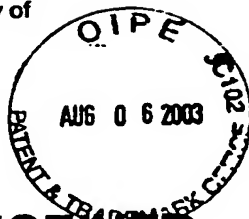
Paper: Transmittal Form (in dup) with certificate of mailing; Power
of Attorney with Revocation & Change of Correspondence Address;
Statement Under 37 CFR 3.73(b) with Table A attached; Copy of
recorded Assignment; return card.

Applicant: P. Dan Cook et al
Title: Compositions & Methods for Enhanced Biostability and
Altered Biodistribution of Oligonucleotides in Mammals
Serial No 09/546,596 Filing Date: April 10, 2000
Docket No. ISIC0006-101 (ISIS-4380)
Date Sent: August 4, 2003
MP Straher/JJiulianti

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Date Sent: August 4, 2003
MP Straher/JJiulianti




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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

<h1>TRANSMITTAL FORM</h1> <p>(to be used for all correspondence after initial filing)</p>	Application Number	09/546,596
	Filing Date	April 10, 2000
	First Named Inventor	P. Dan Cook
	Art Unit	1634
	Examiner Name	J.N. Freeman
Total Number of Pages in This Submission	Attorney Docket Number	ISIC0006-101 (ISIS-4380)

ENCLOSURES (check all that apply)		
<input type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment / Response <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/ Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Assignment Papers (for an Application) <input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input checked="" type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s)	<input type="checkbox"/> After Allowance Communication to Group <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Statement Under 37 CFR 3.73(b) with Table A attached; copy of recorded Assignment
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT	
Firm or Individual name	Michael P. Straher
Signature	
Date	August 4, 2003

CERTIFICATE OF MAILING			
I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.			
Typed or printed name	Michael P. Straher	Date	August 4, 2003
Signature			

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

**POWER OF ATTORNEY WITH REVOCATION AND
CHANGE OF CORRESPONDENCE ADDRESS**

I hereby revoke all previous powers of attorney or authorizations of agent given in the applications identified in Table A attached hereto, and appoint

☒ Practitioners at Customer Number: 34138



as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please change the Correspondence Address for all applications identified in Table

A to:

☒ Practitioners at Customer Number: 34138

I am the:

☐ Applicant/Inventor.

☒ Assignee of record of the entire interest. (A statement under 37 CFR 3.73(b) is enclosed.)

Respectfully submitted,

ISIS PHARMACEUTICALS, INC.

Date: 5-30-03

By: _____

Name: B. Lynne Parshall
Title: Executive Vice President

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

STATEMENT UNDER 37 CFR 3.73(b)

Applicant, **ISIS Pharmaceuticals, Inc.**, a corporation, states that it is:

☒ the assignee of the entire right, title, and interest of the applications identified in Table A attached hereto.

The extent (by, percentage) of its ownership interest is **100%** in the patent applications identified in Table A by virtue of:

☒ a copy of the pertinent assignment from the inventor(s) of the patent applications identified in Table A is enclosed herewith.

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Respectfully submitted,
ISIS PHARMACEUTICALS, INC.

Date: 5-30-03

By: _____

Name: **B. Lynne Parshall**
Title: **Executive Vice President**

TABLE A

SERIAL NO.	FILING DATE	INVENTORS	EXAMINER	ART UNIT	TITLE
09/546,596	April 10, 2000	Cook, Manoharan, Bennett	J.N. Fredman	1637	Compositions and Methods for Enhanced Bioavailability and Altered Biodistribution of Oligonucleotides in Mammals
09/902,953	July 11, 2001	Krolz, Mehta	J.Schultz	1635	Enhancement of the Stability of Oligonucleotides Comprising Phosphorothioate Linkages by addition of Water-Soluble Antioxidants
09/944,493	August 22, 2001	Weinbach, Tillman, Geary, Hardee	Not Yet Determine	1615	Pulsatile Release Compositions and Methods for Enhanced Intestinal Drug Absorption
09/935,316	August 22, 2002	Teng, Weinbach, Tillman, Geary, Hardee	Not yet determined	1632	Bioadhesive Compositions and Methods for Enhanced Intestinal Drug Absorption
10/029,598	December 21, 2001	Teng, Cook, Tillman, Hardee, Ecker, Manoharan	J. Epps	1635	Compositions and Methods for Non-Parenteral Delivery of Oligonucleotides
09/315,294	May 20, 1999	Mehta, Hardee, Cook, Ecker, Tsai, and Templin	M. Schmidt	1635	Compositions and Methods for Topical Delivery of Oligonucleotides
09/315,298	May 20, 1999	Teng, Cook, Tillman, Hardee, Ecker and Manoharan	J. Epps	1635	Compositions and Methods for Non-Parenteral Delivery of Oligonucleotides
09/108,673	July 1, 1998	Teng, and Hardee	W. Sandals	1636	Compositions and Methods for the Delivery of Oligonucleotides via the Alimentary Canal

ISIS 438



Inc/ mps
UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231 *D42*

DECEMBER 28, 2000

PTAS

WOODCOCK WASHBURN KURTZ MACKIEWICZ ET AL
MICHAEL P. STRAHER
1650 MARKET STREET
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PENNSYLVANIA 19103-7301



JAN 02 2001

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

✓RECORDATION DATE: 10/18/2000

✓REEL/FRAME: 011191/0626
NUMBER OF PAGES: 5

✓BRIEF: CROSS-REFERENCING OF ASSIGNMENT FROM PRIOR APPLICATION S.N. 08/928,823 FILED 9/12/97, RECORDED AT REEL 9035/FRAME 0624 ON 3/31/98.

ASSIGNOR:
✓COOK, PHILLIP DAN

DOC DATE: 12/01/1997

ASSIGNOR:
✓MANOHARAN, MUTHIAH

DOC DATE: 12/01/1997

ASSIGNOR:
✓BENNETT, CLARENCE FRANK

DOC DATE: 12/01/1997

ASSIGNEE:
✓ISIS PHARMACEUTICALS, INC.
2292 FARADAY AVENUE
CARLSBAD, CALIFORNIA 92008

SERIAL NUMBER: 09546596
PATENT NUMBER:

FILING DATE: 04/10/2000
ISSUE DATE:

*Reviewed 11 Jan 01
Copy to Client*

011191/0626 PAGE 2

SHARON LATIMER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

11-02-2000

HEET

J.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

To The Honorable Commissioner of
thereof.



101502715

rd the attached original documents or copy

1. Name of conveying party(ies):
Phillip Dan Cook, Muthiah Manoharan and Clarence
Frank Bennett

Additional name(s) of conveying party(ies)
attached? () YES (X) NO

3. Nature of Conveyance:
() Assignment () Merger
() Security Agreement
() Change of Name
(X) Other: Cross-referencing of Assignment from prior
application S.N. 08/928,823 filed 9/12/97, recorded at
Reel 9035/Frame 0624 on 3/313/98
Execution Date(s): December 1, 1997

2. Name and address of receiving party(ies):
Name: ISIS Pharmaceuticals, Inc.

10-18-00
Street Address: 2292 Faraday Avenue
City: Carlsbad
State: California ZIP 92008
Additional name(s) & address attached? () YES (X) NO

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
09/546,596 filed 4/10/00

B. Patent No.(s)

Additional numbers attached? () YES (X) NO

5. Name and address of party to whom correspondence
concerning documents should be mailed:
Name: Michael P. Straher
Internal Address: WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
Philadelphia, Pennsylvania 19103-7301

Street Address: WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
1650 Market Street
Philadelphia, Pennsylvania 19103-7301

6. Total number of applications and patents involved:
One (1)

7. Total fee (37 CFR 3.41):.....\$40.00
(X) Enclosed
() Authorized to be charged to Deposit Account
Number 23-3050

8. Please charge any deficiency or credit any
overpayment to Deposit Account Number 23-3050

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Michael P. Straher/38,325
Name of Person Signing/Reg. No.

Signature

October 12, 2000
Date

Total number of pages including cover sheet, attachments, and document: 5

Mail documents to be recorded with required cover sheet information to:

/02/2000 GTON11 00000004 09546596 Commissioner of Patents and Trademarks
FC:581 40.00 0P Box Assignments
Washington, D.C. 20231

PATENT
Joint Inventors

(Pending Application;
Serial No. Known)

DOCKET NO.: ISIS-2707

A S S I G N M E N T

WHEREAS, we Phillip Dan Cook, Muthiah Manoharan and Clarence Frank Bennett, hereinafter referred to as the assignors, residing respectively at 2124 Acker Way, Escondido, California 92029, 7634 Reposado Drive, Carlsbad, California 92009 and 1347 Cassins Street, Carlsbad, California 92009 are the joint inventors of certain inventions or improvements for which we have made application for Letters Patent to the United States, identified as Serial No. 08/928,823, filed September 12, 1997, entitled COMPOSITIONS AND METHODS FOR ENHANCED BIOSTABILITY AND ALTERED BIODISTRIBUTION OF OLIGONUCLEOTIDES IN MAMMALS; and

WHEREAS, ISIS Pharmaceuticals, Inc. hereinafter referred to as the assignee, of 2292 Faraday Avenue, Carlsbad California 92008, a corporation of Delaware, is desirous of acquiring the entire right, title and interest in and to the said inventions or improvements and in and to the said application, and in, to and under any and all Letters Patent which may be granted on or as a result thereof in any and all countries:

NOW, THEREFORE, for and in consideration of the sum of One Dollar (\$1.00) to each of us in hand paid by said assignee, and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the said assignors, have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over to said assignee, the entire right, title and interest in and to said inventions or improvements and said application and any and all continuations, divisions and renewals of and substitutes for said application, and in, to and under any and all Letters Patent which may be granted on or as a result thereof in the United States and any and all other countries, and any reissue or reissues or extension or extensions of said Letters Patent, and assign to and authorize said assignee, to file in our names applications for Letters Patent in all countries, the same to be held and enjoyed by said assignee, its successors, assigns, nominees or legal representatives, to the full end of the term or terms for which said Letters Patent respectively may be granted, reissued or extended, as fully and entirely as the same would have been held and enjoyed by us had this assignment, sale and transfer not been made.

77

PATENT
Joint Inventors

AND we hereby covenant that we have full right to convey the entire interest herein assigned, and that we have not executed and will not execute any agreement in conflict herewith, and we further covenant and agree that we will each time request is made and without undue delay, execute and deliver all such papers as may be necessary or desirable to perfect the title to said inventions or improvements, said application and said Letters Patent to said assignee, its successors, assigns, nominees, or legal representatives, and each of us agrees to communicate to said assignee or to its nominee all known facts respecting said inventions or improvements, said application and said Letters Patent, to testify in any legal proceedings, to sign all lawful papers to execute all disclaimers and divisional, continuing, reissue and foreign applications, to make all rightful oaths, and generally to do everything possible to aid said assignee, its successors, assigns, nominees and legal representatives to obtain and enforce for its or their own benefit proper patent protection for said inventions or improvements in any and all countries.

AND we hereby authorize and request the Commissioner of Patents and Trademarks of the United States and any official of any country or countries foreign to the United States whose duty it is to issue patents on applications as aforesaid, to issue to said assignee, as assignee of the entire right, title and interest, any and all Letters Patent for said inventions or improvements, including any and all Letters Patent of the United States which may be issued and granted on or as a result of the application aforesaid, in accordance with the terms of this assignment.

IN WITNESS WHEREOF, we have hereunto set our hands and seals.

Phillip Dan Cook (L.S.)
Phillip Dan Cook

Muthiah Manoharan (L.S.)
Muthiah Manoharan

Clarence Frank Bennett (L.S.)
Clarence Frank Bennett

PATENT
Joint Inventors

[WHERE ALL INVENTORS SIGN BEFORE THE SAME NOTARY:]

State of California :
COUNTY OF San Diego : SS

On this 1st day of December, 1997, before me personally came the above named Phillip Dan Cook, Muthiah Manoharan and Clarence Frank Bennett to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.



Kristy Davis
Notary Public

[WHERE INVENTORS SIGN BEFORE SEPARATE NOTARIES:]

COUNTY OF _____ : SS

On this _____ day of _____, 19____, before me personally came the above named Phillip Dan Cook to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.

Notary Public

PATENT
Joint Inventors

_____: SS
COUNTY OF _____:

On this _____ day of _____, 19__, before me personally came the above named Muthiah Manoharan to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.

Notary Public

_____: SS
COUNTY OF _____:

On this _____ day of _____, 19__, before me personally came the above named Clarence Frank Bennett to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.

Notary Public